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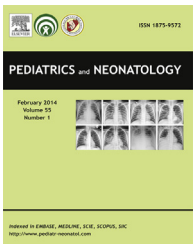

ORIGINAL ARTICLE

Clinical Effectiveness of Aripiprazole in Short-term Treatment of Tic Disorder in Children and Adolescents: A Naturalistic Study

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Background/purpose: The purpose of this study was to evaluate the effectiveness and tolerability of aripiprazole in short-term treatment of children and adolescents with tic disorder (TD).
Methods: This was a 14-week, prospective, open-label flexible dose trial of aripiprazole. We enrolled patients with TD aged between 4 years and 18 years. They received aripiprazole (dose: 2.5 mg/day) initially, which was then adjusted according to clinical response. The severity was assessed by the Yale Global Tic Severity Score (YGTSS) at 0, 2, 6, 10, and 14 weeks. The linear mixed models were used for evaluation of the YGTSSs at each follow-up, which were compared with baseline scores.
Results: Eighty-one patients were enrolled in this study. Nine patients withdrew from the study with complaints of adverse side effects. Of the remaining 72 patients, 15 patients discontinued medications prematurely due to being free of symptoms for over 2 weeks. Two patients discontinued medications due to no significant improvement. The mean scores had significantly decreased since the 2nd week ($p < 0.01$). The mean reduction was 51.0% in the motor tic scores, 67.1% in the vocal tic scores, and 70.0% in the total YGTSSs. The common adverse effects were sedation (32.1%) and increased appetite (22.2%). A slight increase in average body weight was noted, from 32.7 to 33.7 kg (+1.0 kg, $p < 0.05$).

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Conclusion: Aripiprazole is effective for short-term treatment of TD, especially vocal tics, in children and adolescents with mild adverse effects. However, further double-blind trials against placebo or other medications are needed to verify the efficacy of aripiprazole in the pharmacotherapy of TD.

1. Introduction

Tic disorder (TD) is a common childhood-onset neuropsychiatric disorder, characterized by sudden, fast, repetitive, nonrhythmic, and stereotyped motor movements and/or phonic productions. The diagnosis is based on the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition, Text Revision (DSM-IV-TR) criteria (published by the American Psychiatric Association in 2000). Based on the type and duration of tics, it is classified as transient TD, chronic TD, and Tourette syndrome (TS). Common comorbidities of TDs are attention deficit hyperactivity disorder (ADHD), obsessive-compulsive disorder, oppositional defiant disorder, and other mood disorders.[1]

Although the exact pathophysiology of TD remains unclear, potent dopamine D_2 antagonist is the major treatment of tics.[2] Haloperidol and pimozide are the only formally approved medications currently used to treat TD and the drugs can reduce symptoms in approximately 66% and 60% of patients, respectively. However, adverse effects, such as acute dystonic reactions, akathisia, tardive dyskinesia, extrapyramidal syndrome (EPS), and prolonged QTc, are bothersome.[2–5]

Aripiprazole, an atypical antipsychotic medication, has a unique pharmacology, and it plays the role of a dopamine–serotonin system stabilizer rather than the dopamine–serotonin antagonist. It is a partial agonist of D_2 receptors, but it also acts as an antagonist in the presence of excess dopamine. In addition, it is also an agonist of 5-HT_{1A} receptors and an antagonist of 5-HT_{2A} receptors. Theoretically, it might have a lower potential for EPS than other more traditional antipsychotics.[6]

The purpose of this study was to evaluate the short-term effects and tolerability of aripiprazole in children and adolescents with TD.

2. Patients and Methods

This study was a 14-week, prospective, open-label flexible dose trial in children and adolescents with TD receiving monotherapy with aripiprazole.

We enrolled patients between 4 and 18 years of age with transient TD, chronic TD or TS, and symptoms of TD that were severe enough to influence social function, self-esteem, or quality of daily life. Our protocol was approved by the Institutional Review Board. Diagnosis was established based on DSM-IV-TR at the outpatient clinic of the Mackay Memorial Hospital. The patients had been free from medications for tics for at least 3 months before entry. Exclusion criteria were (1) mental retardation; (2) seizure activity; (3) obsessive-compulsive disorder, autism, and other psychiatric illness, except ADHD; (4) combined use of other psychostimulants, mood stabilizers, or anticonvulsants; and (5) allergy to any neuroleptics.

All patients received 2.5 mg aripiprazole (Otsuka Pharmaceutical Co. Tokushima, Japan) at bedtime initially. We offered each patient specific pill master to cut pills into pieces. At each visit, the clinicians adjusted the dose according to clinical response, severity of disease, and adverse effects. The evaluation of adverse effects depended on patients' and their parents' subjective complaints. If adverse effects were not tolerated, aripiprazole was discontinued immediately. If participants were completely symptom free for more than 2 weeks under 2.5 mg/day aripiprazole, early discontinuation of medications was considered.

We used the Yale Global Tic Severity Score (YGTSS), which is widely used with excellent interactive reliability, to evaluate the severity of the disease. This scale consisted of three scores, namely, motor tic (0–25), vocal tic (0–25), and total YGTSSs (sum of motor tic scores, vocal tic scores, and impairment scores; 0–100). The ratings for motor and vocal tics included number, frequency, intensity, complexity, and interference. We rated the YGTSSs and checked body weight of the patients at their first clinical visit as the baseline and then at the 2nd, 6th, 10th, and 14th weeks. The YGTSS was calculated by the same clinician to avoid personal bias.

2.1. Statistical analyses

The results of YGTSSs (including motor tic, vocal tic, and total YGTSSs) were recorded as mean ± standard deviation (SD). The linear mixed models were used for the evaluation of repeated measures for the YGTSSs at each follow-up compared with baseline. The linear mixed model was adjusted for age, gender, diagnosis, and dose. The average of individual body weights at baseline and end point was compared using a paired t test. A p value < 0.05 was taken to be significant. All statistical analyses were performed using SPSS version 17.0 software (SPSS Inc., Chicago, IL, USA).

3. Results

The baseline demographics and diagnosis of the eligible patients ($n = 81$) are listed in Table 1. Nine patients were unable to complete the study protocol due to adverse effects, including sedation ($n = 6$), gastrointestinal upset ($n = 2$), change of appetite ($n = 2$), hand tremor ($n = 1$),

Table 1 Descriptive data for the 81 patients with tic disorder treated with aripiprazole.

Variable	Value
Age (y, mean ± SD)	8.3 ± 3.4
Gender	
Male	60 (74.1)
Female	21 (25.9)
Type of tic disorder	
Tourette syndrome	25 (30.9)
Chronic tic disorder	3 (3.7)
Transient tic disorder	53 (65.4)

Data are presented as *n* (%).
SD = standard deviation.

dizziness ($n = 1$), and quietness ($n = 1$). The discontinuation rate for this study was 11.1%.

Fifty-five patients completed the trial, and 15 patients discontinued aripiprazole before 14 weeks due to being completely symptom free for more than 2 weeks when treated with aripiprazole (2.5 mg/day). Another two patients discontinued aripiprazole at the 6th and 10th weeks due to no significant improvement. The mean motor tic scores were 11.03 ± 5.04, 7.61 ± 5.70, 6.63 ± 5.47, 4.90 ± 5.39, and 5.40 ± 5.42 at baseline and at weeks 2, 6, 10, and 14, respectively. The mean vocal tic scores were 8.51 ± 6.40, 5.59 ± 5.75, 4.52 ± 5.40, 3.61 ± 4.86, and 2.80 ± 4.33 at baseline and at weeks 2, 6, 10, and 14, respectively. The mean impairment scores were 10.56 ± 3.71, 3.71 ± 5.70, 2.09 ± 4.10, 0.82 ± 2.77, and 0.74 ± 2.64 at baseline and at weeks 2, 6, 10, and 14, respectively. The mean total YGTSSs were 30.10 ± 7.35, 16.91 ± 11.45, 13.24 ± 10.98, 9.33 ± 9.04, and 9.04 ± 8.45 at baseline and at weeks 2, 6, 10, and 14, respectively. A significant reduction had been observed since the 2nd week (Table 2). The mean scores had significantly decreased since the 2nd week ($p < 0.01$). Overall, the mean reduction was 51.0% in the motor tic scores, 67.1% in the vocal tic scores, and 70.0% in the total YGTSSs.

The mean dose of aripiprazole during treatment was 2.84 ± 0.48 mg/day, and the maximal dose was 3.23 ± 0.88 mg/day. The dose was unrelated to body weight. In addition, YGTSSs at baseline showed no significant difference among the transient TD (29.74 ± 7.68), chronic TD (30.00 ± 9.90), and TS (34.33 ± 6.85) groups. The YGTSSs at week 14 of the transient TD, chronic TD, and TS groups were 8.35 ± 8.37, 8.50 ± 2.12, and 10.39 ± 9.14, respectively. The degree of improvement was not significantly different in transient TD, chronic TD, and TS.

Most patients tolerated aripiprazole well, and no drug-related EPS was noted in this study. The adverse effects are listed in Table 3. Sedation and increased appetite were the most common adverse effects reported by the patients. Sedation was usually mild without influencing daily life and improved with time or after decreasing dose. Two patients became temperamental, and three patients became better tempered. Other adverse effects were usually mild and improved later or after the discontinuation of medications. There was a slight increase in average individual body weight between baseline and end point, from 32.7 ± 14.9 to 33.7 ± 14.8 kg (+1.0 kg, $p < 0.05$).

4. Discussion

There are two major pharmacotherapies for TD—antipsychotic and nonantipsychotic medications. Although typical antipsychotic medications, such as haloperidol and pimozide, appear to have higher potency for reducing symptoms, they are associated with the risk of severe and unacceptable adverse effects.[5] Sulpiride, a selective dopamine D_2 antagonist, is also effective for treatment of TS and chronic TD. According to our previous study, the severity rate decreased by 49% in motor tic scores, 64% in vocal tic scores, and 59% in total YGTSSs.[7] However, the half-life of sulpiride is short. Therefore, it needs to be taken two times every day, but some patients do not follow this requirement. Atypical antipsychotics, such as risperidone, olanzapine, ziprasidone, quetiapine, and clozapine, have serotonin-blocking effects, but variable D_2-blocking properties with fewer neurological adverse effects. They can reduce symptoms by approximately 35—50%. However, weight gain and metabolic complications, such as hyperprolactinemia and dyslipidemia, are worrisome concerns.[8–12] Among nonantipsychotic medications, clonidine, an α-adrenergic agonist, is widely used and can reduce 26% of symptoms. However, many clinicians are reluctant to use it due to concerns regarding hypotension.[13]

In previous small case series, aripiprazole reduced total YGTSSs by 44.3—56.0%. The improvements in the total

Table 2 Analysis of the YGTSS in motor tic, vocal tic, and total scores by the linear mixed model.

	Motor tic score		Vocal tic score		Total YGTSS	
	β* (SE†)	*p*	β* (SE†)	*p*	β* (SE†)	*p*
Week 0‡	Reference		Reference		Reference	
Week 2‡	−3.48 (0.64)	<0.01	−2.98 (0.60)	<0.01	−13.24 (1.24)	<0.01
Week 6‡	−4.62 (0.77)	<0.01	−4.18 (0.76)	<0.01	−17.15 (1.36)	<0.01
Week 10‡	−6.58 (0.83)	<0.01	−5.32 (0.85)	<0.01	−21.45 (1.42)	<0.01
Week 14‡	−6.21 (0.88)	<0.01	−6.22 (0.92)	<0.01	−22.16 (1.47)	<0.01

The data are adjusted for gender, age, type of tic, comorbidity of ADHD, and drug dose.
ADHD = attention deficit hyperactivity disorder; YGTSS = Yale Global Tic Severity Score.
* β-coefficient.
† Standard error (SE).
‡ Compared with the baseline score.

Table 3 Adverse effects reported by patients treated with aripiprazole.

Adverse effect	*n* (%)
Sedation	26 (32.1)
Increased appetite	18 (22.2)
Decreased appetite	5 (6.2)
Became quiet	5 (6.2)
Gastrointestinal upset	4 (4.9)
Somnambulism	3 (3.7)
Mood lability	2 (2.5)
Dizziness	2 (2.5)
Headache	1 (1.2)

motor and vocal scores were 50.0—61.3% and 56.3—71.4%, respectively.[14—18] The results, which showed greater responsiveness to aripiprazole in vocal tics than in motor tics, were similar to our study. If we compare the TS group and the chronic TD group in our study with our previous study,[7] the dramatic reduction of vocal tic scores in the aripiprazole group was more apparent than the sulpiride group by the 2nd week.

Some authors have suggested that aripiprazole has the potential to treat irritability and aggression, which are the common comorbidities of TD.[19,20] In this study, three patients became better-tempered, whereas two became temperamental after aripiprazole treatment. Because of the lack of a placebo group, it is difficult to differentiate the effects of drug from the nature course.

Furthermore, the dose of aripiprazole in TD was not well-established in pediatric groups due to the limited number of studies. The initial dose of aripiprazole in most previous studies (4.5—20 mg/day) is higher than that of the present study. Children and adolescents might be more susceptible to dose-related side effects of aripiprazole, because of the higher mean peak steady-state concentration and shorter time to required to reach maximum serum concentration of aripiprazole.[21] The use of a higher dosage did result in an increasing incidence of adverse effects, such as sedation (16.7—81.8%), blurred vision (9.0%), and EPS (8.3—63.0%) in previous studies.[14—18] Because the dose was not related to body weight in our study, the specific dose for aripiprazole in treatment of TD could not be established. However, some patients were already responding well to lower doses (2.5 mg/day). Therefore, we suggest administering a lower dose initially and then slowly increasing the dosage based on clinical response.

Patients are often involved in the dilemma of whether to face the tic-related embarrassment or to bear the adverse effects of the medicine, especially traditional antipsychotics. In our study, no serious adverse effects such as EPS were associated with aripiprazole. One-third of the patients encountered sedation, but this resolved with time or decreasing doses. The degree of body weight gain in patients using aripiprazole was lower than those in patients using other atypical antipsychotic medications,[8,9] and part of the body weight gain might be due to normal growth.[22] Previous studies also supported no significant changes of metabolic parameters, and even decreasing QTc interval during aripiprazole treatment.[19,23]

There were some limitations in our study. The natural course of TD is fluctuating, and therefore, it is difficult to differentiate the effects of the drug during the clinical course without having a placebo group. Furthermore, the rate of transient TD in our study was 65.4%; however, the degree of improvement was not different in patients with transient TD, chronic TD, and TS. Third, the severity of infections in the patients was mild to moderate. Therefore, the effectiveness of treatment in severe TDs requires further study.

In conclusion, aripiprazole is effective for the short-term treatment of TD, especially vocal tics, with few adverse effects. However, further double-blind trials against placebo or other medications are needed to verify the role of aripiprazole in the pharmacotherapy of TD.

Conflicts of Interest

The authors declare that they have no financial or non-financial conflicts of interest related to the subject matter or materials discussed in the manuscript.

References

1. Jimenez-Shahed J. Tourette syndrome. *Neurol Clin* 2009;**27**:737—55.
2. Scahill L, Erenberg G, Berlin Jr CM, Budman C, Coffey BJ, Jankovic J, et al. Contemporary assessment and pharmacotherapy of Tourette syndrome. *NeuroRX* 2006;**3**:192—206.
3. Shapiro AK, Shapiro E, Wayne H. Treatment of Tourette's syndrome with haloperidol, review of 34 cases. *Arch Gen Psychiatry* 1973;**28**:92—7.
4. Pringsheim T, Marras C. Pimozide for tics in Tourette's syndrome. *Cochrane Database Syst Rev* 2009;(2):CD006996.
5. Shapiro E, Shapiro AK, Fulop G, Hubbard M, Mandeli J, Nordlie J, et al. Controlled study of haloperidol, pimozide and placebo for the treatment of Gilles de la Tourette's syndrome. *Arch Gen Psychiatry* 1989;**46**:722—30.
6. Bowles TM, Levin GM. Aripiprazole: a new atypical antipsychotic drug. *Ann Pharmacother* 2003;**37**:687—94.
7. Ho CS, Chen HJ, Chiu NC, Shen EY, Lue HC. Short-term sulpiride treatment of children and adolescents with Tourette syndrome or chronic tic disorder. *J Formos Med Assoc* 2009;**108**:788—93.
8. Scahill L, Leckman JF, Schultz RT, Katsovich L, Peterson BS. A placebo-controlled trial of risperidone in Tourette syndrome. *Neurology* 2003;**60**:1130—5.
9. McCracken JT, Suddath R, Chang S, Thakur S, Piacentini J. Effectiveness and tolerability of open label olanzapine in children and adolescents with Tourette syndrome. *J Child Adolesc Psychopharmacol* 2008;**18**:501—8.
10. Caine ED, Polinsky RJ, Kartzinel R, Ebert MH. The trial use of clozapine for abnormal involuntary movement disorders. *Am J Psychiatry* 1979;**136**:317—20.
11. Sallee FR, Kurlan R, Goetz CG, Singer H, Scahill L, Law G, et al. Ziprasidone treatment of children and adolescents with Tourette's syndrome: a pilot study. *J Am Acad Child Adolesc Psychiatry* 2000;**39**:292—9.
12. Mukaddes NM, Abali O. Quetiapine treatment of children and adolescents with Tourette's disorder. *J Child Adolesc Psychopharmacol* 2003;**13**:295—9.
13. Gaffney GR, Perry PJ, Lund BC, Bever-Stille KA, Arndt S, Kuperman S. Risperidone versus clonidine in the treatment of children and adolescents with Tourette's syndrome. *J Am Acad Child Adolesc Psychiatry* 2002;**41**:330—6.

14. Murphy TK, Bengtson MA, Soto O, Edge PJ, Sajid MW, Shapira N, et al. Case series on the use of aripiprazole for Tourette syndrome. *Int J Neuropsychopharmacol* 2005;**8**:489—90.
15. Davies L, Stern JS, Agrawal N, Robertson MM. A case series of patients with Tourette's syndrome in the United Kingdom treated with aripiprazole. *Hum Psychopharmacol* 2006;**21**: 447—53.
16. Yoo HK, Choi SH, Park S, Wang HR, Hong JP, Kim CY. An open-label study of the efficacy and tolerability of aripiprazole for children and adolescents with tic disorders. *J Clin Psychiatry* 2007;**68**:1088—93.
17. Seo WS, Sung HM, Sea HS, Bai DS. Aripiprazole treatment of children and adolescents with Tourette disorder or chronic tic disorder. *J Child Adolesc Psychopharmacol* 2008;**18**:197—205.
18. Lyon GJ, Samar S, Jummani R, Hirsch S, Spirgel A, Goldman R, et al. Aripiprazole in children and adolescents with Tourette's disorder: an open-label safety and tolerability study. *J Child Adolesc Psychopharmacol* 2009;**19**:623—33.
19. Stigler KA, Diener JT, Kohn AE, Li L, Erickson CA, Posey DJ, et al. Aripiprazole in pervasive developmental disorder not otherwise specified and Asperger's disorder: a 14-week, prospective, open-label study. *J Child Adolesc Psychopharmacol* 2009;**19**:265—74.
20. Bastiaens L. A non-randomized, open study with aripiprazole and ziprasidone for the treatment of aggressive behavior in youth in a community clinic. *Community Ment Health J* 2009;**45**: 73—7.
21. Greenaway M, Elbe D. Focus on aripiprazole: a review of its use in child and adolescent psychiatry. *J Can Acad Child Adolesc Psychiatry* 2009;**18**:250—60.
22. de Onis M, Onyango AW, Borghi E, Siyam A, Nishida C, Siekmann J. Development of a WHO growth reference for school-aged children and adolescents. *Bull World Health Organ* 2007;**85**:660—7.
23. Goodnick PJ, Jerry J, Parra F. Psychotropic drugs and the ECG: focus on the QTc interval. *Expert Opin Pharmacother* 2002;**3**: 479—98.